REMARKS

Claims 1-68 constitute the pending claims in the present application. Among them, Claims 2, 17-20, 36-55, and 57-68 are directed to non-elected inventions and/or species, and are withdrawn from further consideration. If necessary, Applicants will cancel claims directed to non-elected inventions and/or species upon indication of allowable subject matter. Claims 1, 3-16, 21-35, and 56 are directed to the elected Group I invention. Applicants thank the Examiner for withdrawing the second species election.

Applicants note that the Information Disclosure Statements filed on October 25, 2004 and August 15, 2005 have been considered by the Examiner.

Applicants have also amended Claims 1, 5, 8, 9, 11, 12, 15, 16, 21, 23, 25, 26, 28, 29, 31, 32, 35, and 56 to correct typographic / grammatical errors, or to clarify the subject matter claimed. Applicants submit that no new matter is introduced due to these amendments, and the amendments do not narrow the scope of the claims.

Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the Office Action.

Specification

The Office Action objects to the specification, because it contains certain embedded hyperlink and/or other form of browser-executable code.

Applicants have amended the specification to modify the references to the browser-executable code, so as to render them not executable by browsers. Reconsideration and withdrawal of the objections are respectfully requested.

The Office Action also objects to the specification for non-compliance with the sequence rules of 37 C.F.R. §§ 1.821 – 1.825.

Applicants have amended the specification to insert appropriate SEQ ID NOs., thereby overcoming this objection. Reconsideration and withdrawal of the objections are respectfully requested.

Claim rejections under 35 U.S.C. § 112, first paragraph - enablement

Claims 1, 3-16, 21-35, and 56 are rejected under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Specifically, the Office Action first runs through the eight *Wands* factors, then contends that the instant specification "lacks any evidence or guidance on how to reliably predict when a [sic] engineered polypeptide will maintain the predicted fold, overall structure, and said catalytic and binding activities when produced in a real-world laboratory environment," and that "the prior art does not [sic] shows only examples where predicted structures can be used only if very close homologs with known structures are available." Thus, the Office Action concludes that only trial and error experimentations can help to "determine if modeled structural characteristics for a given protein are present in empirically determined real-world protein structures," and that such experimentations amounts to undue experimentation. Applicants respectfully disagree.

Applicants submit that the rejection is based on a misunderstanding of the claimed invention, and, as a result, the analysis of the *Wands* factors is incorrect.

The thrust of the rejection is based on the notion that it is difficult to reliably predict the structure / fold of an engineered protein, because "predicted structures can be used only if very close homologs with known structures are available." See, for example, paragraph "e)" on page 7 of the Office Action. To support this view, the Office Action cited Ginalski, which suggests that protein structural prediction from primary sequence information "can be used if very close homologs with known structure are available." Ginalski also suggests that current structure prediction methods do not work very well for quaternary structure prediction (e.g., prediction of protein-protein interaction, or interaction between protein subunits), except for those exhibiting "minimal conformation changes upon complex formation." Ganalski also warns that "substantial errors" may result if go beyond the limits tolerated by such models.

First of all, Applicants submit that the Ginalski comments regarding protein quaternary structure prediction is largely irrelevant with respect to Claims 1 and 21, which are directed to embodiments with a single recipient polypeptide.

Secondly, Applicants submit that Ginalski actually supports, rather than undermines the enablement of the claimed invention. The claimed invention partly relies on the replacement of only a limited number of amino acid residues in the recipient polypeptide, such that the cumulative effect of these substitutions on the overall structure of the recipient polypeptide is minimal. For example, to engineer a serine protease triad into a recipient polypeptide, such as an scFv antibody fragment, at most three amino acids on the recipient polypeptide need to be replaced by a Ser, a His, and an Asp. If the recipient site happens to contain one or more of these three triad amino acids, as few as one amino acid needs to be mutated. Thus, even for a small recipient molecule like scFv (about 200 residues), only 0.5 – 1.5% of the total residues are mutated in the engineered polypeptide. In other words, the engineered polypeptide is 98.5 – 99.5% identical to the original scFv recipient polypeptide, for which structure is known. For a larger recipient molecule, such as a full-length antibody several times the size of an scFv, the % identity is more than 99%.

In addition, since the spatially conserved amino acids are usually (but not necessarily) non-consecutive amino acids, the impact of each substitution on its local environment is expected to be relatively independent, at least as compared to the impact of replacing a stretch of consecutive amino acids.

Finally, since multiple rotamers are usually available for each residue to be substituted into a recipient polypeptide, the side-chains of these substituting residues are not rigid / inflexible. Thus minor clashes with the other recipient polypeptide atoms (such as other binding pocket or catalytic pocket atoms) may be avoided by choosing the right rotamer (see, for example, Example 2 and Figure 2), while major clashes may result in discarding the individual models with such clashes.

In summary, the cited art actually supports the enablement of the claimed invention. Because of the extremely high overall sequence identity between the recipient polypeptide and the engineered polypeptide, the usually dispersed locations of the residues to be substituted in the recipient polypeptide, the flexibility of the substituting residue side-chains, especially the requirement that the second set of amino acid residues in the recipient polypeptide "have a geometric relationship that matches the spatially conserved geometry" of the motif to be "grafted" onto the recipient polypeptide, Applicants submit that the recipient polypeptide can well tolerate the minimal perturbations to its overall structure. The claimed invention is fully

enabled. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph are respectfully requested.

Claim rejections under 35 U.S.C. § 112, second paragraph

Claims 1, 3-16, 21-35, and 56 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Specifically, the Office Action contends that it is unclear whether the claimed method steps include only computer embodiments (wherein the engineered peptide is modeled entirely *in silico*); embodiments wherein an [sic] "real-world" peptide is engineered and produced in a biological laboratory; or embodiments involving both *in silico* modeling and generating a real-world peptide. Applicants respectfully disagree.

The Office Action essentially contends that the claim language can be interpreted to encompass at least these three embodiments. However, the fact that the claim language is broad does not necessarily render it indefinite. MPEP 2173.04 specifically indicates that:

> "Breadth of a claim is not to be equated with indefiniteness. *In re Miller*, 441 F.2d 689, 169 USPQ 597 (CCPA 1971). If the scope of the subject matter embraced by the claims is clear, and if applicants have not otherwise indicated that they intend the invention to be of a scope different from that defined in the claims, then the claims comply with 35 U.S.C. 112, second paragraph."

In fact, Applicants submit that the scope of the claims is clear, because the Examiner correctly interpreted the claims to encompass all three recited embodiments. There is no ambiguity regarding whether a specific embodiment falls within or outside the claim language. Because of this, there is no legal basis for the Examiner to limit the scope of the examination to just one randomly picked embodiment.

Therefore, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, second paragraph.

CONCLUSION

In view of the above amendment, applicant believes the pending application is in condition for allowance. Applicants believe no fee other than the TWO-month extension fee is due with this response. However, if any additional fee is due in connection with the filing of this response, please charge our Deposit Account No. **18-1945**, under Order No. **COTH-P01-002** from which the undersigned is authorized to draw.

Dated: April 14, 2006

Respectfully submitted,

By_____

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